REMARKS

In accordance with the present invention, there are provided transdermal patches comprising granisetron loaded into a defined acrylic adhesive, i.e., an acrylic adhesive which is required to contain non-acidic hydroxyl moieties. As demonstrated in the Examples, the combination of adhesive having non-acidic hydroxyl moieties and granisetron provides numerous advantages, e.g.,

-the combination has been found to be remarkably stable;

-the combination has been found to have surprisingly good drug release properties; and

-the combination has been found to have surprisingly good skin flux properties.

That the invention combination of components should provide at least the above-referenced benefits is all the more surprising, given the teaching of prior art such as Effing (WO 98/53815 A1) to the contrary. Indeed, flux and permeation properties of invention patches are so good that it is not necessary to incorporate additives such as skin permeation enhancers in order to achieve desirable performance properties. This is extremely unusual in skin patches. Indeed, the reduction, or even elimination, of additives such as permeation enhancers also means that there is less chance of patches according to the invention causing skin irritation.

Invention patches are suitable for the delivery of granisetron to a subject in need thereof, and find use, for example, in the treatment or prevention of emesis, such as that caused by the administration of chemotherapy to cancer patients.

By the present communication, claims 1, 7, 9 and 30-32 have been amended, and new claim 34 has been added, to define Applicants' invention with greater particularity. No new matter is introduced by the subject amendments as the new and amended claim language is fully supported by the specification and original claims. Upon entry of the amendments submitted herewith, claims 1-26 and 28-34 will be pending. The present status of all claims in the application is provided in the Listing of Claims presented herein beginning on page 2 of this communication.

Rejection under 35 U.S.C. § 112, second paragraph

The rejection of claim 9 under 35 U.S.C. § 112, second paragraph, as allegedly being indefinite, is once again respectfully traversed. Applicants respectfully disagree with the Examiner's assertion that the phrase "adapted to provide a pharmacologically effective amount of granisetron after about 2 hours" is allegedly unclear (see page 2, lines 11-12 of the Office Action). Contrary to the Examiner's assertion, the language at issue is submitted to be clear. One of skill in the art would readily understand the above-quoted language to indicate that the patch can deliver amounts of the active ingredient, granisetron, capable of doing that which granisetron is known to do, e.g., prevent nausea and vomiting in a subject undergoing chemotherapy, within 2 hours of being administered to the patient; i.e., invention patches can be administered to a patient, and within 2 hours, chemotherapy can start. Consistent with this discussion, the Examiner's attention is directed to paragraph **[0035]** of Applicants' specification, which indicates that "the patches of the present invention can already begin to show efficacy by about 2 hours. . ."

The repeated assertions by the Examiner of alleged lack of clarity of the above-quoted claim language are submitted to be without merit. To the extent drug may be released in less than 2 hours, the amount of drug released does not reach the level required for efficacy until about 2 hours have elapsed.

However, in order to reduce the issues and expedite prosecution, claim 9 has been amended herein to adopt the language acknowledged by the Examiner to be clear, i.e., that invention patches provide a pharmacologically effective amount of granisetron to a subject in need thereof **within** about 2 hours after administration thereof.

Accordingly, reconsideration and withdrawal of the rejection under 35 U.S.C. § 112, second paragraph are respectfully requested.

Rejection under 35 U.S.C. § 102(b)

The rejection of claims 1-26, 28-31 and 33 under 35 U.S.C. § 102(b) as allegedly being anticipated by Effing (WO 98/53815 A1) is once again respectfully traversed. It is respectfully submitted that reliance by the Office on the Effing reference mandates that the reference be considered as a whole, for all that it teaches, not just that which is convenient for the Examiner's purposes. A fair reading of the reference, when taken as a whole, teaches both the interchangeability of tropisetron and granisetron, and the undesirability of using hydroxy-containing monomers (such as 2-hydroxyethylacrylate (HEA)) in the preparation of an adhesive patch containing tropisetron or granisetron.

In contrast to that which is taught by Effing, Applicants' invention, as defined, for example, by claim 1, requires an adhesive patch suitable for the transdermal administration of granisetron (not tropisetron), wherein the adhesive is an acrylic adhesive containing specific functional groups, an adhesive which Effing clearly teaches against, i.e., an acrylic adhesive containing non-acidic hydroxyl moieties. Only Applicants recognize that there are significant structural and/or functional differences between tropisetron and granisetron such that adhesive formulations which are clearly contra-indicated by the art are actually highly effective with the specific active, granisetron.

Specifically, Effing discloses a transdermal patch comprising an adhesive containing A and B monomers. Although granisetron is mentioned as an alternative, the Effing disclosure focuses entirely on tropisetron. Indeed, the Effing Examples make no mention of granisetron.

The unwavering focus of Effing on tropisetron is demonstrated in the Examples and the concomitant effect on the description. Effing Example 7 is the only Example that employs an adhesive having a nucleophilic group, and is shown to lose 10% of its tropisetron content after just 4 weeks storage at room temperature. It is of note that the adhesive employed in Effing Example 7 is the only adhesive employed by Effing that causes reduction in tropisetron content

of the resulting patch, tropisetron being stable in all of the other adhesives tested. In direct contrast, in Table 5 of Example 2 of Applicants' disclosure, it is shown that granisetron was not only stable in the preferred (nucleophilic) adhesive at low temperature (5°C), but was stable at room temperature (25°C) for a far longer period of time than was evaluated by Effing (i.e., 6 weeks); indeed, granisetron was observed to be stable for 6 weeks at an elevated temperature of 40°C.

As a result of Effing's failure to recognize any significant structural and/or functional differences between tropisetron and granisetron, the Effing teaching is directed to adhesive patches containing either tropisetron or granisetron. As previously noted, throughout the Effing disclosure, it is suggested that these two compounds are substantially similar both structurally and functionally (see, for example, page 1, line 23-page 2, line 2 of Effing, which suggests the interchangeability of these compounds). Indeed, as previously noted, virtually every reference to active drug in the Effing specification is made in the alternative:

-in the Title ("TROPISETRON OR GRANISETRON");

-in the abstract, line 5 ("selected from the group consisting of tropisetron and granisetron");

-in the abstract, line 7 ("tropisetron or granisetron");

-page 1, line 6 of the specification ("tropisetron or granisetron");

-page 1, lines 23-24 of the specification ("Tropisetron . . . and granisetron");

-page 2, line 20 of the specification ("tropisetron and granisetron");

-page 2, line 28 of the specification ("tropisetron and granisetron"); and

-page 7, line 24 ("tropisetron or granisetron").

The only exceptions throughout the Effing specification where tropisetron and granisetron are not mentioned in the same clause are found:

-in the background (at page 2, line 10) where "ondansetron and granisetron" are suggested to be interchangeable; and

-in the Examples, which deal only with tropisetron; however, based on the consistent indication throughout the Effing specification that tropisetron and granisetron are substantially interchangeable, there is no reason (absent improper reliance on Applicants' disclosure) why one of skill in the art would expect granisetron to perform any differently than tropisetron.

Moreover, not only does Effing teach the interchangeability of tropisetron and granisetron, the reference also teaches the undesirability of using hydroxy-containing monomers (such as HEA) in the preparation of an adhesive patch containing tropisetron or granisetron. Indeed, the reference clearly teaches away from the use of any hydroxy-containing monomer, such as HEA, in the preparation of an adhesive patch containing tropisetron or granisetron, as evidenced by the numerous admonitions throughout the Effing specification that the B monomer should be free of nucleophilic groups (including hydroxyl moieties):

-page 3, line 24 of the specification ("Preferably, the B monomer is free of nucleophilic groups");

-page 3, line 30 – page 4, line 1 ("Preferably, the B monomer is free of nucleophilic groups");

-page 4, lines 8-9 ("Such monomers are preferably free of groups containing nucleophilic groups as described above");

-claim 2, lines 1-2 ("said B monomers are free of nucleophilic groups");

-claim 3 lists numerous possible B monomers, but hydroxy-containing monomers are conspicuously absent from the list of possibilities;

-claim 12, lines 1-2 ("said B monomers are free of nucleophilic groups"); and

-claim 13 lists numerous possible B monomers, but hydroxy-containing monomers are conspicuously absent from the list of possibilities.

Thus, repeatedly throughout their disclosure, Effing asserts that "preferably, the B monomer is free of nucleophilic groups."

Indeed, the numerous admonitions throughout the Effing specification that the B monomer should be free of nucleophilic groups are fully consistent with the results of EXAMPLE 7 (at page 13 of Effing), which indicates that an adhesive prepared with 2-hydroxyethylacrylate (HEA) as monomer B suffered from a decrease in drug content of more than 10% within only four weeks of storage at room temperature. This stands in stark contrast to the remaining examples which evaluate the stability of the active drug in the transdermal patch. See, for example, EXAMPLE 1 and EXAMPLE 2 (both at page 11 of Effing), which indicate that full stability is retained at both 25°C and 40°C for at least four weeks with the adhesive formulations employed therein (which include no hydroxy-containing monomers).

Furthermore, of the numerous examples of B monomers set forth at page 3, lines 11-23 of Effing, only one contains a free hydroxyl group (2-hydroxyethylacrylate, HEA). One can question, however, why that compound is even included in the list of suitable monomers, since, as noted above, the reference, when read in its entirety, makes it clear that use of such a B monomer is disfavored.

Since all of the experiments conducted by Effing are carried out with tropisetron, Effing makes the erroneous assumption that whatever applies to tropisetron applies also to granisetron—and merely extrapolates the results with tropisetron to granisetron. Nowhere is granisetron distinguished in any way from tropisetron, and only tropisetron is exemplified. The catastrophic storage experiment with tropisetron (Effing Example 7) results in a very specific teaching away from the use of adhesives containing nucleophilic groups with either tropisetron or granisetron (see page 3 of the Effing disclosure). This comes immediately after a paragraph replete with examples of numerous exemplary B monomers, only one of which contains a nucleophilic group, which is then promptly taught away from as a result of the highly undesirable result therewith.

In view of Effing's teachings, one of skill in the art would expect that observations made with respect to tropisetron (the only compound with which Effing conducted experiments) would

be equally applicable to granisetron. This clearly teaches against the present invention since Effing makes it clear that the only B monomer disclosed therein that contains a free hydroxyl group (2-hydroxyethylacrylate, HEA) is disfavored. Thus, one of skill in the art would have no motivation to use a hydroxy-containing monomer such as HEA in the preparation of an adhesive patch containing tropisetron or granisetron. Even if such motivation existed, based on the teachings of Effing, one of skill in the art would have no expectation of success using tropisetron or granisetron with an adhesive such as the adhesive of Effing Example 7. Accordingly, the results reported herein are both surprising and unexpected in view of the teachings of Effing.

It is respectfully submitted that the assertion of the Effing reference against the present claims can only be maintained by engaging in improper hindsight analysis, having benefit of Applicants' disclosure. Indeed, it is only upon engaging in improper hindsight analysis that the Examiner can advance the argument that Effing in any way suggests doing that which Applicant has done. Such use of Applicants' disclosure is clearly improper. It is, therefore, resepectfully submitted that a fair reading of Effing, when taken as a whole, actually teaches against that which only Applicants have demonstrated to be of therapeutic value, i.e., adhesive patches suitable for the transdermal administration of granisetron, wherein the adhesive is an acrylic adhesive containing non-acidic hydroxyl moieties, with a physiologically effective amount of granisetron being loaded in the adhesive.

Thus, to the extent the Examiner elects to rely on the Effing reference, the reference must be considered as a whole, for all that it teaches, not just that which is convenient for the Examiner's purposes. When read as a whole, the reference not only teaches the interchangeability of tropisetron and granisetron, the reference also teaches the undesirability of using hydroxy-containing monomers such as HEA in the preparation of an adhesive patch containing tropisetron or granisetron.

The various points raised by the Examiner at pages 6-7 of the Advisory Action in efforts to support the rejection under 35 U.S.C. § 102(b) over Effing are each misplaced for at least the following reasons. With respect to point i), i.e.,

> i) Effing does teach the use of the claimed compound for the same purpose, namely, granisetron in an adhesive patch for the transdermal administration;

. . . while the Examiner's assertion that "Effing does teach the use of . . . granisetron in an adhesive patch for the transdermal administration" (emphasis added) is correct, it is not relevant to the invention as claimed herein—which requires granisetron in a specific adhesive patch, i.e., a patch comprising a defined acrylic adhesive and granisetron. As discussed in detail above, Effing clearly teaches against the adhesive required by the present claims (i.e., an adhesive containing non-acidic hydroxyl moieties). Moreover, nowhere in Effing is there any specific teaching of a patch comprising granisetron and an adhesive containing a nucleophilic group. Indeed, there is no incentive for the skilled person to make such a patch. Since the nearest to such a patch described by Effing is Example 7, which quite specifically teaches that patches containing adhesives with nucleophilic groups have unacceptable storage qualities, one of skill in the art would clearly have no incentive to make a patch such as required by the present claims.

With respect to point ii), Applicants respectfully disagree with the Examiner's assertion that:

> ii) Effing does teach the use of the claimed non-acidic hydroxyl moieties such as 2-hydroxyethylacrylate (see page 3, lines 13-14).

What Effing actually teaches is the undesirability of using non-acidic hydroxyl moieties with an active agent such as tropisetron or granisetron. The highly undesirable results presented in Effing Example 7 cannot be ignored. One of skill in the art would readily understand that that example clearly teaches away from the combination described therein (i.e., tropisetron or granisetron in combination with a non-acidic hydroxyl moiety).

With respect to point iii), i.e.,

> iii) applicant compares the stability of the claimed invention and that of Effing, however, the present claims do not require any storage conditions, let alone the specific storage condition taught in example 7 of Effing;

. . . it is respectfully submitted that the excellent storage stability of invention patches is an inherent property thereof, and clearly represents a feature which was not achieved or recognized by Effing. In spite of the fact that this is an inherent property of invention patches, in order to reduce the issues and expedite prosecution, claim 1 has been amended herein to make specific reference to the storage stability of invention patches.

With respect to point iv),

> iv) although the claims are interpreted in light of the specification, limitations from the specification are not read into the claims. See *In re Van Geuns*, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993);

. . . it is respectfully submitted that the claims stand on their own—with no need to import limitations from the specification.

With respect to point v), Applicants respectfully disagree with the Examiner's assertion that "v) example 7 discloses stability study for tropisetron, not granisetron." It is respectfully submitted to be improper for the Examiner to continue to ignore the clear teachings of the cited art, i.e., that tropisetron and granisetron are interchangeable components, and that the use of hydroxy-containing monomers (such as 2-hydroxyethylacrylate (HEA)) in the preparation of an adhesive patch containing tropisetron or granisetron is undesirable.

With respect to point vi), the Examiner's observation that

> vi) dependent claim 7 of the present application recites that the adhesive patch further comprises *a major amount of a primary acrylate monomer*, leaving the amount for the non-acidic hydroxyl moiety, indeed, minor

is submitted to be irrelevant. Those of skill in the art are well aware of the fact that the primary monomer (in a functionalized polymer) is usually present at significantly higher levels than the functional monomer, which in this case, is the non-acidic hydroxy-containing monomer. Those of skill in the art are also well aware of the fact that the functional monomer is pivotal in determining the chemical and physical characteristics of the resulting adhesive. Hence the Examiner's suggestion that the non-acidic hydroxy-containing monomer is somehow less relevant because it exists in significantly smaller quantities than the primary monomer is without merit.

Furthermore, regardless of how little, or how much of the non-acidic hydroxyl moiety is present, the present claims clearly require the presence of such component, whereas Effing clearly teaches against the presence of such component. One cannot have a more clear contrast between the claimed subject matter relative to the prior art.

Moreover, in order to reduce the issues and expedite prosecution, the claims as amended herein require a specific amount of the primary acrylate monomer, and a specific amount of the non-acidic hydroxyl moiety (see especially claims 1 and 7).

Point vii) of the Advisory Action, i.e.,

> vii) example 2 of the present specification does not disclose the structure of the patch, *e.g.*, what monomer, what non-acidic hydroxyl moieties, and in what amounts were used for the stability study. In contrast, Effing at page 3, line 14 teaches B monomer includes HEA. Applicant directs the Examiner's attention to example 7 in Effing for the teaching of the storage stability, it is noted that example 7 is directed to a different compound, e.g., tropisetron. Further, a reference may be relied upon for all that it would have reasonably suggested to one having ordinary skill in the art, *including nonpreferred embodiments*. Merck & Co. v. Biocraft Laboratories, 874 F.2d 804, 10 USPQ2d (Fed. Cir.), cert. denied, 493 U.S. 975 (1989). Moreover, it is noted that the claimed adhesive patch is not entirely composed of HEA, per se. This is evident by claims 7 and 8 of the present invention, which recite a patch that "containing a *major* amount of a primary acrylate monomer" selected from either 2-

> ethylhexyl acrylate or butyl acrylate. These polymers do not contain non-acidic hydroxyl moieties.

advances several arguments that are without merit.

For example, the Examiner's assertion that "example 2 of the present specification does not disclose the structure of the patch" is clearly erroneous. The Examiner's attention is directed to the fact that Example 2 makes specific reference to the use of DT 2287, a commercially available adhesive of known content. For the Examiner's convenience, a copy of the manufacturer's Product Data Sheet for DT 2287 is provided herewith. The appended material provides substantial detail regarding the patch employed in the example, i.e., the monomers employed, what non-acidic hydroxyl moieties were employed, and in what amounts these components were used.

As further evidence of the well-known nature of the materials employed in example 2 of the present specification, the Examiner's attention is directed to U.S. Patent Application Publication No. US 2005/0208116 A1, at paragraph **[0062]**, where Duro Tak 87-2287 (National Starch) is identified as an example of a functional pressure sensitive adhesive. See also U.S. Patent Application Publication No. US 2006/0039960 A1, at paragraph **[0021]**, where Durotak 387-2287 is identified as an exemplary adhesive for use in the preparation of a transdermal therapeutic system.

Thus, taken with that which was known in the art at the time the present application was filed, there is no merit to the Examiner's assertion that "example 2 of the present specification does not disclose the structure of the patch."

The Examiner's further assertion that Effing's "example 7 is directed to a different compound, e.g., tropisetron" ignores the fact that a fair reading of the reference, when taken as a whole, teaches the interchangeability of tropisetron and granisetron. There is every reason to believe that the Effing experimental results with tropisetron would be similarly obtained with granisetron. Moreover, Effing provides no reason to doubt that granisetron would behave

substantially the same as tropisetron. Thus, if use of an hydroxy-containing monomer is contra-indicated for tropisetron, such use would also be contra-indicated for granisetron. No other conclusion is reasonable from the Effing disclosure.

With respect to the question of what a reference may be relied upon for, it is respectfully submitted that the Examiner has failed to apply the very standards which have been set forth in the passage quoted above. Specifically, it is only appropriate for the Examiner to apply Effing "for all that it would have reasonably suggested to one having ordinary skill in the art . . ." (emphasis added). Based on the teachings of Effing, when taken as a whole, it is respectfully submitted to be unreasonable to ignore the catastrophic storage experiment (Effing Example 7), which clearly teaches away from the use of adhesives containing nucleophilic groups with either tropisetron or granisetron.

The Examiner's assertion "that the claimed adhesive patch is not entirely composed of HEA, per se" is not relevant. As noted above, regardless of how little, or how much of the non-acidic hydroxyl moiety is present, the present claims clearly require the presence of such component, whereas Effing clearly teaches against the presence of such component.

Accordingly, reconsideration and withdrawal of the rejection under 35 U.S.C. § 102(b) are respectfully requested.

Rejection under 35 U.S.C. § 103(a)

The rejection of claim 32 under 35 U.S.C. § 103(a), as allegedly being unpatentable over Effing in view of Sanger et al. (WO 94/01095 A2), is once again respectfully traversed. Applicants' invention, as defined by claim 32, distinguishes over the applied art by requiring a method of treatment employing the adhesive patch of claim 1, i.e., an adhesive patch suitable for the transdermal administration of granisetron, wherein the adhesive is an acrylic adhesive containing non-acidic hydroxyl moieties, a physiologically effective amount of granisetron being

loaded in the adhesive. Therefore, invention adhesive patches are required to contain hydroxyl moieties, but not just any hydroxyl moieties—non-acidic hydroxyl moieties.

As noted above, Effing does not disclose or suggest such a patch. As further noted above, a fair reading of Effing, when taken as a whole, actually teaches against that which only Applicants have demonstrated to be of therapeutic value, i.e., adhesive patches suitable for the transdermal administration of granisetron, wherein the adhesive is an acrylic adhesive containing non-acidic hydroxyl moieties, with a physiologically effective amount of granisetron being loaded in the adhesive.

Further reliance on Sanger is unable to cure the deficiencies of Effing, since Sanger adds nothing to the consideration of what a transdermal patch for the delivery of granisetron should look like.

Accordingly, reconsideration and withdrawal of the rejection under 35 U.S.C. § 103(a), are respectfully requested.

Conclusion

In view of the above amendments and remarks, reconsideration and favorable action on all claims are respectfully requested. In the event any matters remain to be resolved in view of this communication, the Examiner is encouraged to call the undersigned so that a prompt disposition of this application can be achieved.

Respectfully submitted,

Date November 6, 2008

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Enclosure: Durotak Product Data Sheet for DT 2287